II. REMARKS

Formal Matters

Claims 30-41 are pending after entry of the amendments set forth herein.

Claims 1, 2, 6-14, 16-18, 20-22, and 25-29 were examined and were rejected.

Claims 1, 2, 6-14, 16-18, 20-22, and 25-29 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 30-41 are added. Support for new claims 30-41 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations of the Substitute Specification: claim 30: paragraphs 0084-0098; Figures 3A and 3B; paragraph 0044; and paragraphs 0066-0069; claim 31: paragraph 0071; claim 32: paragraph 0046; claim 33: paragraph 0048; claim 34: paragraphs 0049 and 0050; claim 35: paragraph 0070; claim 36: paragraphs 0084-0098; claims 37-39: paragraph 0072; and claims 40 and 41: paragraphs 0041 and 0044. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Stacy Chen for the courtesy of telephonic interviews which took place on February 17, 2011 and March 3, 2011, and which were attended by Examiner Chen and Applicants' representative Paula A. Borden.

During the interviews, the outstanding rejections were discussed.

Applicants note with gratitude that, as set out in the Interview Summary mailed March 2, 2011, the obviousness-type double patenting rejection over U.S. Patent Nos. 7,198,934 and 6,440,422 has been withdrawn.

Withdrawn rejections

Applicants note with gratitude that the following rejections, raised in the March 1, 2010 Office Action, have been withdrawn:

1) Rejection of claims 14 and 15 under 35 U.S.C. §112, second paragraph;
2) Rejection of claim 10 under 35 U.S.C. §112, second paragraph;
3) Rejection of claims 11, 12, and 18 on the ground of obviousness-type double patenting over certain claims of U.S. Patent No. 7,049,145; and
4) The provisional rejection of claims 1, 2, and 6-25 on the ground of obviousness-type double patenting over certain claims of U.S. Patent Application No. 11/375,159.

Objection to the specification

The specification was objected to. The Office Action stated that the specification fails to provide antecedent basis for the claim limitation regarding vaccines which "do not comprise an adjuvant."

Paragraph 0069 of the Substitute Specification is amended, as noted above.

As noted previously, in the protocol and results described in paragraphs 0084-0098, no adjuvant was used. Thus, these paragraphs provide adequate support for the phrase "wherein the vaccine does not comprise an adjuvant." It is noted that the paragraphs describing the experiments and results relating to Figures 3A and 3B note that in some instances, an adjuvant was used. Thus, where no adjuvant is mentioned, no adjuvant was used. It is standard, where a vaccination protocol is described, to indicate when an adjuvant is used. It is not standard to indicate what is missing from a solution. As such, no new matter is added by the amendment to the Substitute Specification at paragraph 0069.

Paragraph 0070 of the Substitute Specification is amended to state that administration of a vaccine according to the instant disclosure does not require administering a DNA prime or a DNA booster. The immunization protocols described in paragraphs 0084-0098 do not involve a DNA prime or a DNA booster. As such, no new matter is added by the amendment to the Substitute Specification at paragraph 0070.

Claim objection

Claims 22 and 27 were objected to for minor typographical errors.

Claims 22 and 27 are cancelled without prejudice to renewal, thereby rendering any objection to claims 22 and 27 moot.

Rejection under 35 U.S.C. §103(a)

Claims 1, 2, 6-14, 16-18, 20-22, and 25-29 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Schneider et al. ((1998) *Nat. Med.* 4:397; "Schneider") in view of Yang et al. ((1997) *Vaccine* 15:1303-1313; "Yang"), Kumar et al (April, 2002) *Immunology Letters* 81:13-24), and Bujard et al. (WO 98/14583; "Bujard").

New claim set

Claims 1, 2, 6-14, 16-18, 20-22, and 25-29 are cancelled without prejudice to renewal; and a new claim set is provided. Support for the new claims is found in claims 1, 2, 6-14, 16-18, 20-22, and 25-29, and throughout the specification, and noted above.

New claims 30-36 recite a vaccine comprising a recombinant MVA virus comprising a nucleotide sequence encoding *P. falciparum* merozoite surface protein-1 (MSP-1) fragments, where the fragments are:

i) p42 and p38; or

ii) p83, p30, p42, and p38.

Claim 30 also recites that the vaccine does not include an adjuvant.

The cited art does not disclose or suggest a vaccine comprising a recombinant MVA encoding the recited **combinations of MSP-1 fragments**.

Furthermore, the cited art does not disclose or suggest a vaccine comprising a recombinant MVA encoding MSP-1 fragments, where the vaccine **does not include an adjuvant**.

MVA is reported to be a highly attenuated virus, compared to, e.g., vaccinia virus. As such, it would not have been obvious to make a vaccine comprising a recombinant MVA, as recited in claim 30, wherein the vaccine does not comprise an adjuvant.

New claims 35 and 36 recite a method for therapy of malaria, the method comprising administering the vaccine of claim 30. Claim 36 recites that the method does not comprise administering a DNA prime or a DNA booster. As noted above, the cited art neither discloses nor suggests a vaccine as recited in claim 30. Thus, none of the cited art discloses or suggests a method of treating malaria, the method comprising administering the vaccine of claim 30. Furthermore, the art appears to require administration of a DNA prime and/or a DNA booster. As provided in the instant disclosure, a subject vaccine obviates the need for a DNA prime or a DNA booster.

The cited art does not disclose or suggest the instant invention as claimed.

As described below, the cited art, taken together, does not disclose or suggest all of the claim limitations the instant claims. For example, the cited art does not disclose or suggest a vaccine comprising recombinant MVA virus comprising at least one nucleic acid coding for: i) *Plasmodium falciparum* MSP-1 p42 and -38; or iii) *Plasmodium falciparum* MSP-1 p83, p30, p42, and p38, where the vaccine does not comprise an adjuvant.

Schneider

As discussed amply in the November 23, 2009 response[1], **Schneider**, which is the primary reference, discusses **sporozoite** antigens, **not merozoite** antigens.

Schneider discusses Plasmodium species that are not relevant to human malaria.

As discussed in the instant specification, there are four malaria species that infect humans: *Plasmodium malariae*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium falciparum*, with *Plasmodium falciparum* being responsible for almost all fatal infections. Specification, paragraph 0004.

Schneider relates to immunization of mice with antigens (other than MSP-1) from *Plasmodium berghei*. *Plasmodium berghei* does not infect humans; instead, *Plasmodium berghei* is used to generate models of rodent malaria. Schneider, page 397, column 1, second paragraph. **Schneider is thus not relevant to a recombinant virus comprising a nucleic acid encoding *Plasmodium falciparum* antigens.**

Schneider discusses Plasmodium antigens that are not merozoite surface proteins.

When an individual is bitten by a mosquito that carries malaria, sporozoites present in the material injected into the individual by the mosquito enter the bloodstream of the individual and migrate to the liver. Sporozoites infect liver cells, where they multiply into merozoites, rupture the liver cells, and escape back into the bloodstream. Merozoites in the bloodstream infect red blood cells, where they develop into ring forms, then trophozoites (a feeding stage), then schizonts (a reproduction stage), then back into merozoites.

Schneider discusses use of plasmid DNA or MVA vectors encoding *Plasmodium berghei* pre-erythrocytic antigens (thromobspondin-related adhesive protein (**PbTRAP**) and the circumsporozoite protein (**PbCSP**)) to immunize mice against challenge. Both the TRAP and the circumsporozoite proteins are **sporozoite** stage proteins.

The MSP-1 complex of *P. falciparum* constitutes a major component at the surface of the erythrocyte-invading (**merozoite**) form of the parasite.

Thus, Schneider relates to proteins from a different stage of the *Plasmodium* life cycle than MSP-1.

Schneider indicates that use of MVA is not always successful in inducing protective immunity.

Schneider states that various prime-boost immunization strategies, with combination of various

[1] The "November 23, 2009 response" is the amendment, filed on November 23, 2009 and responsive to the July 21, 2009

recombinant vaccinia virus strains and plasmid DNA, were tested for immunogenicity and protective efficacy. Schneider, page 397, column 2, first full paragraph. Schneider states that using plasmid DNA priming an recombinant MVA boosting, complete protection against sporozoite challenge was observed in two different mouse strains. Schneider states that "[t]his specific order of immunization **was essential for protection**." Schneider, page 397, column 2, first full paragraph, emphasis added. As shown in Table 1a of Schneider, use of MVA encoding PbCSP and PbTRAP for the first (priming) and second (boosting) immunizations resulted in very low protection; and use of MVA encoding PbCSP and PbTRAP for the first immunization, followed by use of plasmid DNA encoding PbCSP and PbTRAP for the second immunization, resulted in **no** protection.

Schneider noted that studies carried out in chimpanzee also involved priming with DNA (i.e., plasmid DNA encoding PbCSP and PbTRAP), followed by boosting with MVA (i.e., MVA encoding PbCSP and PbTRAP).

Thus, not only does Schneider not disclose or suggest all of the features of claim 1, Schneider in fact teaches away from use of MVA as a suitable vector for *P. falciparum* antigens.

Kumar

Also as discussed in the November 23, 2009 response, **Kumar** discusses preparation of a DNA plasmid (**not a virus**) encoding the C-terminal 42-kDa region of merozoite surface protein 1 ($pMSP1_{42}$), and preparation of a recombinant vaccinia virus vector encoding the same C-terminal 42-kDa region.

The data contained in Kumar relate to the effect of **immunization with a DNA plasmid encoding MSP-1 p42** ($pMSP1_{42}$). Kumar, bridging sentence, pages 14-15; and page 15, column 1, section 2.1.1. under "Materials and Methods." In connection with the recombinant vaccinia virus (which was not MVA) construct encoding the same C-terminal 42-kDa region, Kumar states that this recombinant vaccina virus was used **to infect target cells for CTL analysis**. Kumar, page 15, column 2, section 2.2 under "Materials and Methods."

Furthermore, the only discussion in Kumar that relates to "the use of viral vectors for the purpose of boosting a primary administration of different antigenic composition, such as a plasmid vaccine" is in the general discussion, e.g., the Introduction (Kumar, page 14, column 2, paragraphs 2 and 3). Kumar states that one way of improving an immune response to a DNA vaccine is to first prime by immunizing with DNA, followed by exposure to antigen. Kumar states that two experiments were conducted: 1) a plasmid encoding the rhesus GM-CSF protein, mixed with a DNA plasmid encoding *P. falciparum* $MSP1_{42}$ was used; and 2) a DNA plasmid

encoding *P. falciparum* $MSP1_{42}$ in combination with recombinant human GM-CSF was used. Kumar **does not provide any experiments showing the use of viral vectors for the purpose of boosting a primary administration of different antigenic composition, such as a plasmid vaccine**.

Yang

Yang discusses use of a recombinant vaccinia virus encoding a 190 kDa merozoite surface antigen, with or without anchor and signal sequences. Yang **does not disclose or suggest any recombinant virus encoding *fragments* of MSP-1**.

Yang neither discloses nor suggests:

- a recombinant **MVA virus** comprising at least one nucleic acid coding for a *Plasmodium falciparum* antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for **at least one fragment** of *P. falciparum* MSP-1, where the at least one fragment is selected from: **i) p42; ii) p42 and p38; and iii) p83, p30, p42, and p38**.

The Office Action stated that the merozoite antigen is processed into fragments (30, 38, and 42 kDa), and stated that each gene was inserted into the thymidine kinase region of the vaccinia virus. Office Action, bridging sentence, pages 10 and 11. The Office Action appeared to imply that genes encoding the 30, 38, and 42 kDa fragments were inserted into the vaccinia virus in Yang. **They were not**.

Yang discusses a recombinant vaccinia virus encoding a C-terminal fragment (**amino acids 1047-1640**) region of MSP-1. Yang, page 1304, column 1, last 8 lines of first full paragraph.

> erythrocytes[26]. An anti-idiotype antibody derived from 2B10 recognized the C-terminal (1047–1640aa) region of MSA1 in a Western blot[26] and appears to recognize the same site on glycophorin A as the merozoite. Here we describe the effect of signal and anchor sequences on the biochemical processing and antibody response to this C-terminal region of MSA1 when expressed by a rVV.

Yang states that the C-terminal fragment is encoded by nucleotides 3553-5280 of the sequence set forth in GenBank Accession No. X02919. Yang, Table 1 and legend. As shown in Exhibit 1,[2] nucleotides 3553-5280 of the X02919 sequence encode amino acids 1047-1621 of MSP-1. As shown in Figure 1 of the instant application, and as depicted schematically in Figure 6A of Kauth et al. (2003) *J. Biol. Chem.* 278:22257 (of record), amino acids 1047-1621 of MSP-1 **does not correspond to any of the MSP-1 fragments recited in claim 1**. Instead, as

[2] Exhibit 1 was provided along with the amendment, filed on November 23, 2009 and responsive to the July 21, 2009 Office

shown in Exhibit 2,[3] amino acids 1047-1621 of MSP-1 begins within p38 and includes most of the amino acid sequence of p42. Thus, Yang discusses a fragment that is not p42, p38, p30, or p83.

Yang does not disclose or suggest a recombinant MVA virus comprising a nucleic acid encoding the particular recited fragments of *P. falciparum*.

Yang mentions in passing that MVA has been developed as an expression vector and shown to be equivalent to replication competent vaccinia virus in several vaccine models.

However, one cannot necessarily extrapolate from vaccinia virus to MVA. First, as noted previously, MVA is highly attenuated, compared to vaccinia virus. It was not necessarily predictable, based on the results of Yang with vaccinia virus, that recombinant MVA comprising a nucleic acid encoding fragments of *Plasmodium falciparum* MSP-1 would be efficacious.

Indeed, Schneider indicated that recombinant MVA encoding *P. berghei* pre-erythrocytic antigens, when administered to mice, in some instances provided no protection at all against challenge.

Bujard

Bujard is entitled "Method for producing recombinants intended for use in a complete malaria antigen GP190/MSP1." Bujard discusses a nucleic acid encoding the complete malaria antigen, where the nucleic acid has a reduced AT content relative to wild-type sequence.

Bujard neither discloses nor suggests:

- a **recombinant MVA virus** comprising at least one nucleic acid coding for a *Plasmodium falciparum* antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for **at least one fragment** of *P. falciparum* MSP-1, where the at least one fragment is selected from: **i) p42; ii) p42 and p38; and iii) p83, p30, p42, and p38**.

One cannot necessarily extrapolate from vaccinia virus to MVA.

The Office Action appears to be of the position that it would be obvious to substitute MVA for vaccinia virus. However, one cannot necessarily extrapolate from vaccinia virus to MVA. First, as noted previously, MVA is highly attenuated, compared to vaccinia virus. It was not necessarily predictable, based on the results of Yang

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Action.

[3] Exhibit 2 was provided along with the amendment, filed on November 23, 2009 and responsive to the July 21, 2009 Office Action.

with vaccinia virus, that recombinant MVA comprising a nucleic acid encoding fragments of *Plasmodium falciparum* MSP-1 would be efficacious.

Indeed, Schneider indicated that recombinant MVA encoding *P. berghei* pre-erythrocytic antigens, when administered to mice, in some instances provided no protection at all against challenge.

The Office has not established a prima facie case of obviousness.

As noted above, the cited art does not disclose or suggest all of the claim elements as recited in claim 1. Furthermore, in contrast to the Office Actions' assertions, the cited art does not provide motivation to make the modification suggested in the Office Action, because the references do not "teach a successful vaccine" where the vaccine would comprise a recombinant MVA comprising a nucleic acid encoding at least one fragment of *P. falciparum*.

As noted above, Schneider teaches that a recombinant MVA encoding *P. berghei* pre-erythrocytic antigens (thromobspondin-related adhesive protein and the circumsporozoite protein) in some instances **failed to induce protective immunity in mice**. As such, one skilled in the art, given Schneider, would **not** have had a reasonable expectation of success, as asserted in the Office Action. Therefore, recombinant MVA vector as claimed, or a vaccine composition comprising same, is **not** simply a predictable combination of prior art elements.

Furthermore, none of the cited art teaches or suggests a recombinant MVA virus comprising a nucleic acid encoding the MSP-1 fragments recited in claim 1. Schneider does not even discuss MSP-1 or any other merozoite antigens, but instead discusses sporozoite antigens. Yang does not discuss any of the recited fragments. Instead, Yang discusses a C-terminal MSP-1 fragment that is different from any of the recited fragments. Kumar discusses use of a recombinant vaccina virus (not a recombinant MVA virus) encoding MSP-1 p42, to infect target cells for CTL analysis. For immunization, Kumar used a plasmid vector encoding MSP-1 p42. Bujard discusses a recombinant vector encoding full-length (p190) MSP-1. Thus, the cited art does not disclose the combination of elements recited in claim 1.

The cited art does not disclose or suggest all of the claim elements of claim 1. Furthermore, Schneider teaches away from the proposed combination. Thus, the recombinant MVA vector as claimed, or a vaccine composition comprising same, is **not** simply a predictable combination of prior art elements. As such, Schneider, alone or in combination with Yang, Kumar, and Bujard, cannot render any of claims 1, 2, 6-14, 16-18, 20-22, and 25-29 obvious.

Conclusion as to the rejection under 35 U.S.C. §103(a)

Applicants submit that the rejection of claims 1, 2, 6-14, 16-18, 20-22, and 25-29 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Nonstatutory double patenting

Claims 1, 2, 6-14, 16-18, 20-22, and 25-29 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-8, 12-19, and 23-31 of U.S. Patent No. 7,198,934, or of claims 1-5, 8-11, 16-19, 24-28, 31, and 33 of U.S. Patent No. 6,440,422, in view of the teachings of certain cited art.

Applicants note with gratitude that, as set out in the Interview Summary mailed March 2, 2011, the obviousness-type double patenting rejection over U.S. Patent Nos. 7,198,934 and 6,440,422 has been withdrawn.

Claim 17 was provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-10 and 21-24 of co-pending U.S. Patent Application No. 12/523,023.

Claim 17 is cancelled without prejudice to renewal, thereby rendering this rejection of claim 17 moot.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number MBPP-004.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 30, 2011

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